Community-Acquired, Methicillin-Resistant and Methicillin-Susceptible *Staphylococcus aureus* Musculoskeletal Infections in Children

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Background: The clinical characteristics and virulence factors related to musculoskeletal infections caused by community-acquired, methicillin-resistant *Staphylococcus aureus* (MRSA) in children are not well-defined.

Methods: In this retrospective study, the demographics, hospital course and outcome of children with musculoskeletal infections were reviewed from medical records and by contacting patients or their physicians. Antimicrobial susceptibilities were determined by disk diffusion. Polymerase chain reaction was performed to detect genes encoding for virulence factors. Mann-Whitney, χ^2 and Kaplan-Meier tests were used for statistical analysis.

Results: Community-acquired MRSA and community-acquired methicillin-susceptible *S. aureus* (MSSA) caused musculoskeletal infections in 31 and 28 children, respectively. The median numbers of febrile days after start of therapy were 4 and 1 for MRSA and MSSA patients, respectively ($P = 0.001$). The median numbers of hospital days were 13 and 8 for the MRSA and MSSA groups, respectively ($P = 0.014$). At follow-up, 2 patients in the MRSA and 1 in the MSSA group had developed chronic osteomyelitis. *pvl* and *fnbB* genes were found in 87 and 90% versus 24 and 64% in the MRSA versus MSSA groups, respectively. ($P = 0.00001$ and 0.017). Ten patients with *pvl*-positive strains had complications versus no patients with *pvl*-negative isolates ($P = 0.002$).

Conclusions: Febrile days and hospital days were greater in children with musculoskeletal infection caused by MRSA than in those affected by MSSA, but no significant differences were found in the final outcome. *pvl* and *fnbB* genes were more frequent in the MRSA than in the MSSA strains. The presence of the *pvl* gene may be related to an increased likelihood of complications in children with *S. aureus* musculoskeletal infections.

Key Words: *Staphylococcus aureus*, methicillin resistance, musculoskeletal infections

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Staphylococcus aureus is the most common etiology of musculoskeletal infections in pediatric patients.[1] For many years, methicillin-resistant *S. aureus* (MRSA) has been an important etiology of osteoarticular infections acquired in the nosocomial setting, primarily in premature infants in neonatal intensive care units.[2] Until recently, the antibiotic treatment of osteoarticular infections caused by *S. aureus* acquired in the community was straightforward, because virtually all *S. aureus* isolates were susceptible to β-lactam antibiotics. However, during the past 5 years methicillin-resistant *S. aureus* has emerged as a major pathogen in the community (CA-MRSA) in many areas of the United States and around the world.[3–8] Although skin and soft tissue infections predominated in the initial descriptions of the clinical spectrum of infections caused by CA-MRSA, increasing numbers of children with invasive infection caused by CA-MRSA have been reported.[6,8–11]

CA-MRSA harboring the genes encoding Panton-Valentine leukocidin (PVL) have been associated with a severe course and poor prognosis in patients with pneumonia.[12–13] In a comparative molecular analysis of community- or hospital-acquired MRSA isolates, differences were found in the frequency of genes encoding for the superantigen toxins.[14]

We hypothesized that the demographics, clinical characteristics, hospital course and outcome for children with musculoskeletal infections caused by CA-MRSA and community-acquired methicillin-susceptible *S. aureus* (MSSA) would be different. In addition, we hypothesized that the presence of selected genes encoding adhesion and virulence

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factors might explain the differences between MRSA and MSSA strains with respect to complications or outcome.

MATERIALS AND METHODS

From February 2000 through December 2002, excluding the month of May 2000 and the period between September 2 and October 15, 2000, community-acquired *S. aureus* strains were collected during prospective surveillance at Texas Children's Hospital. Clinical and antibiotic susceptibility information for children from whom these strains were isolated was recorded on a standardized form. Patients with osteomyelitis, septic arthritis or pyomyositis were selected, and their medical records were reviewed. Diagnosis was based on compatible symptoms and signs, radiographs, radioisotope scan, computed tomography and magnetic resonance imaging. All patients had a positive culture of the affected tissue and/or positive blood culture for *S. aureus*. The diagnosis of chronic osteomyelitis was based on imaging studies and/or histopathology. Deep venous thromboses were documented by Doppler studies. Only patients with community-acquired *S. aureus* infection were included in this study. Community-acquired infection was defined as isolation of *S. aureus* within 72 h of hospitalization. In 2 patients, the diagnosis was established after 72 h, but clinical evidence suggested that it was community-acquired (bone cultures from surgery done 4 days after admission). Patients with an underlying illness such as immunodeficiency (n = 1), cystic fibrosis (n = 1), chronic skin disorder (n = 3), chronic renal failure (n = 1) or history of malignancy (n = 2) were excluded.

From the medical records, we obtained demographic and clinical information (dates of admission, discharge, last visit, clinical course, hospital days, febrile days ≥100.4°F, days of positive blood cultures in patients with bacteremia, surgical treatment, underlying medical conditions and outcome at the time of the discharge and during the follow-up). Chronic osteomyelitis, deep venous thrombosis and fracture at the site of infection were considered complications of osteomyelitis. The parents and/or the primary physician of children with osteomyelitis for whom information after the hospital discharge was not available in the record were contacted by telephone and were asked about additional hospitalizations, surgical or medical treatment, signs of infection and ability to perform normal activities. Information pertaining to antibiotic therapy (initial and final antibiotic, dosage and duration of treatment) was obtained. The study protocol was reviewed and approved by The Institutional Review Board of Baylor College of Medicine. Informed consent was not required.

Laboratory Methods. Isolates were identified as *S. aureus* by standard methods.[15] Screening for methicillin resistance was performed by disk diffusion using a 1-μg oxacillin disk and by growth on Mueller-Hinton agar containing 4% NaCl and oxacillin (6 μg/ml), after an incubation period of 24 h at 35°C, using National Committee for Clinical Laboratory Standards (NCCLS) methodology.[16] Antibiotic susceptibility was performed by the disk diffusion method and interpreted according to the NCCLS guidelines. The antibiotics tested included vancomycin, clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), erythromycin, gentamicin and penicillin. Results were determined after 24 h of incubation at 35°C according to NCCLS breakpoints.[17]

For all isolates that were erythromycin-resistant and clindamycin-susceptible, detection of the inducible macrolide-lincosamide-streptogramin B (MLS_B) resistance phenotype was performed and interpreted by disk diffusion with clindamycin and erythromycin disks set 15–20 mm apart (D test).[18]

Detection of Genes Encoding for Methicillin Resistance and Virulence Factors. DNA was extracted from all *S. aureus* strains. The following genes were detected: *clfA, cna, fnbB, mecA, pvl* and *tst.* Primers and PCR conditions are presented in Table 1.

Statistical Analysis. To compare differences between groups, the Mann-Whitney *U* test was used for continuous variables without normal distribution and the χ^2 or Fisher exact test was used for dichotomous variables. Statistically significant genes were included in a logistic regression model to determine their association with complications. The free-of-disease time (absence of clinical signs and symptoms of bone infection and no evidence of radiographic signs of chronic infection) was calculated by the Kaplan-Meier method, with establishment of diagnosis as initial time and censoring at the time that chronic osteomyelitis was documented or last patient contact. The log rank test was used for testing differences between groups. All analyses were 2-tailed and $P < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS for Windows software version 10.0 (1999).

RESULTS

Clinical Characteristics. During the February 2000–December 2002 study period, community-acquired *S. aureus* was isolated from 59 patients with musculoskeletal infections; 31 had MRSA and 28 had MSSA infections. As part of a previous study of clindamycin treatment of invasive infections, we reported the outcome at the time of hospital discharge for 46 of the patients included in this study.[11] In this report, we include the outcome after follow-up of several months for these 46 patients. We have added 13 patients who presented to Texas Childrens Hospital through December 2002.

No significant differences were found in demographic characteristics or type of infection between MRSA and MSSA groups (Table 2). Surgical interventions were per-

TABLE 1. PCR: Primers and Conditions for Amplification*

Gene	Primer	Oligonucleotide Sequence (5′→3′)	Positive Control (Isolate No.)	$MgCl_2$ (mM)	PCR Cycling
mecA	Mec A1 Mec A2 (Del Vedchio et al[19])	5′-TAG AAA TGA CTG AAC GTC CG-3′ 5′-TTG CGA TCA ATG TTA CCG TAG-3′	1†	3.5	95°C, 1 min; 55°C, 30 s; 72°C, 1 min
cna	cna-oc1 cna-oc2 (Cho et al[20])	5′-GCG GAT CCG CAC GAG ATA TTT CA-3′ 5′-CGG TCG ACT TAT TCA GTA TTA GTA ACC AC-3′	UAMS-1‡	3.0	95°C, 1 min; 63°C, 30 s; 72°C, 1 min
fnbB	fnb B1 fnb B2 (Rozen)‡	5′-GAA AAC ACA AAT TGG GAG CG-3′ 5′-TCC TGC CTT AAT TCC TTC TCC-3′	8325-4	3.5	92°C, 1 min; 55°C, 30 s; 72°C, 2 min
clfA	clf A1 clf A2†	5′-CGA TTG GCG TGG CTT CAG-3′ 5′-GCC AGT AGC CAA TGT CAC-3′	8325-4‡	3.5	92°C, 30 s; 58°C, 30 s; 72°C, 2 min
pvl	pvl 1 pvl 2 (Lina et al[21])	5′-ATC ATT AGG TAA AAT GTC TGG ACA TGA TCC-3′ 5′-GCA TCA AAT GTA TTG GAT AGC AAA AGC-3′	584§	1.5	94°C, 30 s; 55°C, 30 s; 72°C, 30 s
tst	tst 1 tst 2 (Rozen‡)	5′-GTA AGC CCT TTG TTG CTT GC-3′ 5′-TGT GGA TCC GTC ATT CAT TG-3′	ATCC5165	1.5	95°C, 1 min; 57°C, 30 s; 72°C, 1 min

*Amplification was performed in a PTC-200 Peltier thermal cycler PCR System (MJ Research, Reno, NV). The polymerase chain reaction products were separated on a 1.5% agarose gel in 1× 40 mM Tris-acetate, 1 mM EDTA buffer and detected by staining with ethidium bromide.

†Clinical organisms obtained at Texas Children's Hospital.

‡These primers were designed using the Primer3 available at the worldwide web (http://www.genome.wi.mit.edu/genome_software/other/primer3.html).

‡Provided by Dr Mark Smeltzer.

§Confirmed by DNA sequencing.

TABLE 2. Demographic and Clinical Similarities of Patients with Community-Acquired MRSA and MSSA Musculoskeletal Infections at Texas Children's Hospital, 2000–2002*

Clinical Characteristics	MRSA (n = 31)	MSSA (*n* = 28)
Age		
Mean ± SD	7.9 ± 4.8	7.4 ± 5.1
Median; (range) (yr)	7.0; 0.75–18.6	5.8; 0.1–16.0
Gender		
Male	19 (61.2)†	17 (60.1)
Race		
African-American	10 (32.3)	9 (32.1)
Caucasian	11 (35.5)	4 (14.3)
Hispanic	10 (32.3)	13 (46.4)
Asian	—	1 (3.7)
Other	—	1 (3.7)
Type of infection		
Osteomyelitis	26 (83.9)	22 (78.6)
Femur	9	5
Tibia	9	6
Others‡	6	10
Septic arthritis	3 (9.7)	3 (10.7)
Pyomyositis	2 (6.4)	3 (10.7)
Surgical interventions	28 (90.3)	23 (82.1)

*All comparisons were not significant by the Mann-Whitney and χ^2 tests.

†Numbers in parentheses, percent.

‡MRSA, fibula, calcaneous, vertebra, iliac bone, finger, toe; MSSA, humerus (2), sternum (2), fibula, calcaneous, vertebra, iliac bone, scapula, toe.

formed in a high percentage of patients in both groups. Patients with pyomyositis and infections of large bones underwent between 1–4 surgical interventions. No surgical interventions were performed in patients with infection localized to the finger, toe, sternum and vertebra or in children whose bone infection did not require drainage based on imaging studies.

Antibiotic Treatment. Twenty-five, 19 and 15 patients received vancomycin, clindamycin or a β-lactam, respectively, as their initial therapy. After changing the initial empiric treatment, on the basis of antibiotic susceptibility pattern, a total of 28 children (24 and 4 in the MRSA and MSSA groups, respectively) received clindamycin (40 mg/kg/day) as their definitive antistaphylococcal therapy. Six patients received vancomycin (40 mg/kg/day) as their final therapy. Resistance to clindamycin (n = 1) and persistent positive blood cultures (n = 3) were the reasons for using vancomycin; in 2 cases, the reason was undocumented. TMP-SMX was used in 1 patient in the MRSA group for the treatment of chronic osteomyelitis. A β-lactam (nafcillin 150 mg/kg/day or cefazolin 100 mg/kg/day) was used in the final treatment of 23 children with MSSA infections. In the MSSA group, 1 patient empirically treated with clindamycin received a change to TMP-SMX because inducible clindamycin resistance was documented for the patient's isolate (D test). The reason for changing to TMP-SMX instead of a β-lactam was not documented. One patient in the MSSA group was changed from clindamycin to nafcillin because of irritability during intravenous clindamycin infusion.

The duration of the antibiotic treatment varied with the diagnosis for medians of 23 days (range, 21–56 days), 25 days (range, 21–42 days) and 40 days (range, 28–142 days) for patients with pyomyositis, septic arthritis and osteomyelitis, respectively. After hospital discharge patients with

uncomplicated osteomyelitis received home-based intravenous antibiotics to complete 4–6 weeks of therapy. The durations of follow-up (mean ± SE) for patients treated with clindamycin or a β-lactam were similar; 18 ± 1.3 months and 20 ± 1 month, respectively ($P = 0.57$). No differences were found in the time (in months) from the diagnosis of bone infection until presentation of chronic osteomyelitis based on methicillin susceptibility of isolates or the antibiotics received.

Three patients in the MRSA group had a histopathologic diagnosis of chronic osteomyelitis established shortly after admission and were not included in the Kaplan-Meier analysis. All had clindamycin-susceptible MRSA isolates and received that antibiotic intravenously for 6 weeks. Oral clindamycin was used in the long term therapy. During follow-up of children included in the Kaplan-Meier analysis, 3 other children developed chronic osteomyelitis, 2 during clindamycin and one during β-lactam therapy.

Susceptibility Profiles. The antibiotic susceptibility profiles are shown in Table 3. With the exception of resistance to erythromycin that was significantly greater ($P = 0.0001$) in the MRSA group, the antibiotic susceptibilities were similar between groups. Although 25 of 31 (81%) and 4 of 28 (14%) of the MRSA and MSSA isolates were erythromycin-resistant, the MLS_B clindamycin-resistant phenotype was found in only one of the strains in each group.

Genes Encoding for Virulence Factors. When comparing the frequency of genes encoding for virulence factors between groups (Table 4), a greater proportion of MRSA isolates carried the *pvl* and *fnbB* genes than the MSSA isolates ($P = 0.00001$ and 0.017, respectively). No significant differences were found in the frequency of the *clfA* gene. Although not statistically significant, a greater proportion of MSSA isolates than MRSA isolates tested positive for the *tst* gene (20 and 3%, respectively) and the *cna* gene (16 and 40%, respectively). All community-acquired MRSA isolates were *mecA*-positive.

TABLE 3. Antibiotic Susceptibility Profiles of Community-Acquired *Staphylococcus aureus* Isolates Recovered From Children With Musculoskeletal Infections, 2000–2002

Antibiotic	MRSA (n = 31)		MSSA (n = 28)	
	S	R	S	R
Erythromycin*	6 (19)†	25 (81)	24 (86)	4 (14)
Clindamycin	30 (97)	1 (3)	27 (97)	1 (3)
TMP-SXM	30 (97)	1 (3)	28 (100)	—
Gentamicin	31 (100)	—	28 (100)	—
Vancomycin	31 (100)	—	28 (100)	—
Penicillin	—	31 (100)	2 (7)	26 (93)

*χ^2 test, erythromycin susceptibilities for MRSA versus MSSA isolates, $P = 0.0001$.
†Numbers in parentheses, percent.

TABLE 4. Genes Encoding for Virulence Factors in *Staphylococcus aureus* Isolates From Children With CA-MRSA and Community-acquired MSSA Musculoskeletal Infections, 2000–2002

Genes Encoding for Virulence Factors	MRSA (n = 31)	MSSA (n = 25)	P*
pvl	27 (87)†	6 (24)	0.00001
cna	5 (16)	10 (40)	0.06
fnbB	28 (90)	15 (64)	0.017
tst	1 (3)	5 (20)	0.056
clfA	29 (93)	21 (84)	0.25
mecA	31 (100)	0 (0)	0.0001

*χ^2 test.
†Numbers in parentheses, percent.

The number of hospital and febrile days were significantly greater in the MRSA group (median, 13 versus 8, $P = 0.007$ and 4 versus 1; $P = 0.001$) (Table 5). The proportion of patients with complications was equal in the MRSA and MSSA groups. However, when comparing the proportion of patients who presented with complications or developed complications with the presence or absence of the *pvl* gene (Table 6), a greater proportion of children had complications in the *pvl*-positive group (30.3% versus 0.0%; $P = 0.002$). No other virulence genes were associated with complications. When *pvl*, *fnbB* and *mecA* genes were included in a logistic regression model with complications as dependent variable and presence or absence of genes as independent variables, only *pvl* remained significant ($P = 0.003$; 95% confidence inter-

TABLE 5. Hospital Course and Outcome of Children with Musculoskeletal CA-MRSA and Community-acquired MSSA Infections, 2000–2002

Outcome	MRSA (n = 31)	MSSA (n = 28)	P
Cure/improvement at discharge	31	28	NS
Complications			
Chronic osteomyelitis at admission	3	0	NS
Fracture	0	1*	
Chronic osteomyelitis at follow-up	2	1	
Deep venous thrombosis	4	1	
Febrile days			
Mean ± SD	4.9 ± 3.6	1.5 ± 1.8	0.001
Median; range	4; 0–14	1; 0–5	
90% afebrile by day	8	3	
Hospital days			
Mean ± SD	14.5 ± 7.5	12.7 ± 11.7	0.014
Median; range	13; 5–37	8; 4–44	
Days of positive blood cultures	n = 14	n = 11	
Mean ± SD	1.7 ± 2.8	1.6 ± 1.1	0.24
Median; range	2; 0–11	1; 1–4	

*This patient had chronic osteomyelitis deep venous thrombosis and a fracture.

TABLE 6. Complications in Children With Musculoskeletal Infections Caused by Community-Acquired *Staphylococcus aureus* Isolates Containing or Lacking the *pvl* Gene, 2000–2002

Outcome	pvl-Positive (n = 33)	pvl-Negative (n = 23)	*P*
No. of patients with complications.	10	0	0.002
Chronic osteomyelitis at admission	3	0	
Chronic osteomyelitis noted first on follow-up	3	0	
Deep venous thrombosis	5*	0	
Febrile days			
Mean ± SD	4.2 ± 3.6	2.1 ± 2.5	0.017
Median; range	4; 0–14	2; 0–10	
Hospital days			
Mean ± SD	13.5 ± 7.9	14.7 ± 12.3	0.64
Median range	12; 4–37	10; 4–44	
Days of positive blood cultures	n = 15	n = 9	
Mean ± SD	3.7 ± 3.2	1.8 ± 1.3	0.16
Median; range	3; 1–11	1; 1–4	

*One patient had both chronic osteomyelitis and deep venous thrombosis.

val, −0.50 to −0.11), suggesting that *pvl* is associated with complications independent of methicillin susceptibility.

DISCUSSION

The emergence of CA-MRSA as a cause of bone infections has complicated the conventional management of these infections in children. The treatment of acute bone infections caused by CA-MSSA generally has consisted of a 4- to 6-week course of intravenous plus oral β-lactam antibiotic therapy; surgical intervention is performed when appropriate.[1,22]

In 1999, Gwynne-Jones and Stott[8] reported intensive bone involvement and poor outcome at 1-year follow-up in 2 of 4 children with osteomyelitis caused by CA-MRSA in children. In our study, 3 of 45 (6.6%) children with osteomyelitis who had a good outcome at the time of hospital discharge[11] developed chronic infection during follow-up. Chronic osteomyelitis occurred despite early surgical drainage and appropriate antibiotic treatment.

Clindamycin has traditionally been considered an alternative in the treatment of osteoarticular infections caused by methicillin-susceptible *S. aureus*, particularly for patients allergic to or intolerant of β-lactam antibiotics.[23] Our data also support the use of clindamycin as a suitable treatment of osteomyelitis caused by CA-MRSA when the isolate is fully susceptible to this antibiotic. The percentage of clindamycin resistance in both MRSA and MSSA isolates circulating in our area is below 10%, and the inducible MLS_B phenotype is not frequent, allowing us to use this antibiotic as empiric treatment of infections possibly caused by *S. aureus* or as definitive therapy for patients with CA-MRSA infections (excluding endocarditis). In areas with high frequency of clindamycin resistance and/or a high proportion of the inducible-MLS_B phenotype in their community *S. aureus* strains, the empiric use of clindamycin for the treatment of invasive infections is not appropriate but remains a good option for definitive therapy when the isolates are fully susceptible to clindamycin. The efficacy of oral administration of clindamycin for completing treatment of CA-MRSA osteomyelitis should be no different than that for intravenous administration.

No differences were found when we compared the presence of complications between MRSA and MSSA groups. However, the isolates from the 3 patients who developed chronic osteomyelitis during the follow-up as well as the isolates from the patients in whom a diagnosis of chronic osteomyelitis was established during the initial evaluation and the isolates from children with deep venous thrombosis all harbored the *pvl* gene. None of the patients with *pvl* negative isolates had these complications. PVL belongs to the family of synergohymenotropic toxins. When intradermally injected in rabbits, PVL induces severe inflammatory lesions leading to capillary dilatation, chemotaxis, polymorphonuclear infiltration, polymorphonuclear karyorrhexis and skin necrosis.[24] *S. aureus* isolates harboring the *pvl* gene have been associated with primary skin infections and pneumonia.[12,13,21] To our knowledge, our observation is the first to suggest a possible association of the *pvl* gene with the development of complications in children with musculoskeletal infections caused by *S. aureus*.

Deep venous thrombosis (DVT) has been occasionally reported in association with *S. aureus* bone and joint infections.[25,26] All 5 children with DVT in our study were free of hematologic abnormalities. The finding that the 5 children with DVT in our study were infected with *S. aureus* isolates carrying the *pvl* gene suggests a possible role for PVL in the pathogenesis of DVT in CA-*S. aureus* bone infection.

In conclusion, in this study we confirmed the good outcome of patients with bone infection treated with clindamycin when the CA-MRSA strains are fully susceptible to this antibiotic. No differences were found in the final outcome of patients with community-acquired MRSA or MSSA musculoskeletal infection. The presence of the *pvl* gene was associated with more frequent complications of osteomyelitis such as DVT and chronic osteomyelitis in our patients. The influence of virulence factors on the duration of fever and development of complications for musculoskeletal infections caused by CA-MRSA should be studied further.

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